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Adaptation of renal tubule in uremia

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The demonstration that single nephron function can be studied in vitro proved to be an important advance in unravelling the mechanisms of adaptation which occur in various models of experimental renal disease. The fact that a specific nephron segment could be isolated and studied in a controlled environment meant that it was possible to separate those adaptations of function intrinsic to the tubular epithelial cells from those that are dependent upon factors in the uremic milieu. This concept is illustrated in Figure 1 and forms the basis of the approach which we have taken to study nephron function in the chronically diseased kidney.

This review will focus upon studies performed on isolated perfused renal tubules in experimental models of chronic renal failure.

Proximal tubule adaptations

Fluid reabsorption. This has been studied in the solitary remnant kidney of the uremic rabbit, that is, unilateral nephrectomy plus partial infarction of one kidney plus contralateral nephrectomy. An important feature of this model of disease, which has been employed in numerous studies of renal failure in other species, is the fact that the remaining renal parenchyma undergoes significant compensatory hypertrophy. This is characterized not only by structural enlargement of individual components of the nephron but also by marked increases in single nephron filtration rate and in the absolute rate of proximal tubular fluid reabsorption in vivo [1]. Since structural enlargement of the reabsorbing surface of the tubule, an increased tubule-fluid flow-rate, and an alteration in peritubular physical factors could all account for the increased absolute rate of proximal tubular fluid reabsorption in this model, it is only by removing the nephron segment from its immediate environment that the intrinsic properties of the tubular epithelium can be evaluated.

Studies on the isolated superficial proximal straight tubule from remnant kidneys revealed a significant increase in tubule size as evidenced by increased internal and external diameters and by an increase in dry weight per unit length [2]. Comparable studies on segments from remnant kidneys obtained from rabbits in which the contralateral kidney was left in situ did not show this hypertrophy. Measurement of fluid reabsorption in vitro revealed a significant increase in net fluid reabsorption (Fig. 2) which correlated well with the degree of hypertrophy. This increase was not seen in the nonuremic remnant kidneys. The fact that comparable rates of fluid reabsorption were observed whether the tubules were bathed in normal or uremic rabbit serum pointed to the fact that the adaptation was intrinsic to the tubular epithelium and reflected either an increased rate of sodium transport or decreased back-leak into the tubular lumen [2].

An extension of these studies was carried out on the superficial, late proximal convoluted tubule (S_2 segment) from remnant kidneys, in which there is an increase in single nephron filtration rate, and in embolized kidneys in which the filtration rates of individual nephrons was decreased uniformly by the injection of microspheres into one renal artery [3]. In these studies it was found that net fluid reabsorption per unit length was increased by 60% in the remnant kidney proximal tubules and decreased by 50% in those obtained from embolized kidneys. This was associated with an increase in transepithelial potential difference in the former and a decrease in the latter. The potential differences measured in the remnant kidney tubules (-6.6 ± 0.8 mV) are significantly greater than those recorded in the normal superficial proximal convoluted tubule under any other experimental circumstances. Associated with these changes in transport and potential difference there was a reversal of the normal Na:Cl permselectivity of the tubule. P_{Cl} is greater than P_{Na} in the late superficial proximal convoluted tubule; this was reversed in both experimental models so that $P_{Na} > P_{Cl}$. Whereas significant hypertrophy was again observed in the remnant kidneys, a decrease in tubule size was not evident in the embolized kidneys.

Taken together, these studies indicate the existence of tubular "memory," that is, the pattern of transport which obtains in vivo persists when the tubule is studied in vitro. While hypertrophy can account for an increased rate of fluid absorption in a model of disease in which single nephron filtration rate is increased, reabsorptive surface area does not appear to be the critical determinant of fluid reabsorption when filtration rate is decreased. Some factor, which is not the rate of flow of tubular fluid nor the uremic milieu nor the size of the tubule, links the rate of filtration to the intrinsic capacity of the proximal tubule to reclaim filtrate in the chronically diseased kidney.

Phosphate transport. Adaptations in the intrinsic pattern of phosphate handling have been documented recently in preliminary studies on the proximal straight tubules of uremic rabbits with remnant kidneys [4, 5]. When these uremic rabbits are maintained on an ad lib intake of normal laboratory chow, they

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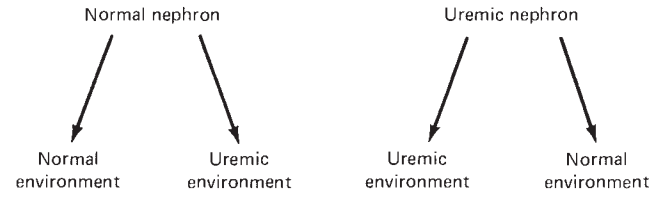

Fig. 1. *Principle of the experimental design which allows normal and uremic nephron segments to be studied in vitro in either a normal or a uremic environment.* This is achieved by bathing and perfusing the nephron segment in serum and ultrafiltrate obtained from normal and uremic rabbits.

do not appear to develop secondary hyperparathyroidism, whereas biologically active parathyroid hormone levels increase when they are maintained on a high phosphorus intake. Net fluid reabsorption is increased consistently but is dissociated from net phosphate reabsorption which is increased only in the uremic euparathyroid tubules. Unidirectional flux measurements revealed that this increase was due to an increase in lumen-to-bath phosphate flux [4].

The fact that in vitro fluid and phosphate reabsorption are dissociated and that the latter increases only under specific in vivo conditions [related perhaps to circulating parathyroid hormone (PTH) levels or directly to the phosphorus intake] suggests that this is a true adaptation rather than being a nonspecific concomitant of the uremic state. These findings indicate that an intrinsic pattern of phosphate transport is "programmed" into the function of the tubule but that modulation by extratubular factors may occur in vivo.

The possibility that the sensitivity of the end-organ to PTH could be altered in uremia was also studied. When the effects of 1-34 bPTH on lumen-to-bath phosphate flux, were examined, it was found that there was increase in the sensitivity to PTH in the euparathyroid uremic animals and a decrease in sensitivity in the hyperparathyroid uremic animals [5]. The dose-response curve was shifted by an order of magnitude to the left and to the right, respectively, in the two uremic groups. Maximal inhibition (of approximately 30%) was, however, the same in the normal and the uremic tubules.

Taken together, these findings strongly suggest the existence of an adaptation at the level of the PTH receptor in uremia with "up-regulation" in the euparathyroid state and "down-regulation" in the hyperparathyroid state. Indeed no differences in the dose-response curves are seen with dibutyryl cAMP (Yanagawa and Fine, unpublished observations), confirming that the adaptation of the tubular response to PTH in the rabbit occurs at a cellular step prior to the generation of cAMP.

Adaptations in the cortical collecting tubule

Water permeability and the response to vasopressin. Numerous explanations have been advanced for the inability of patients and experimental animals with chronic renal failure to generate a maximally concentrated urine. One of these is a blunted or absent response of the cortical collecting tubule to vasopressin. On the other hand, the ability of uremic patients to generate a maximally dilute urine appears to persist further into the course of renal disease. For this to occur the diluting segment must be intact and the collecting tubule must remain impermeable to water in the absence of vasopressin.

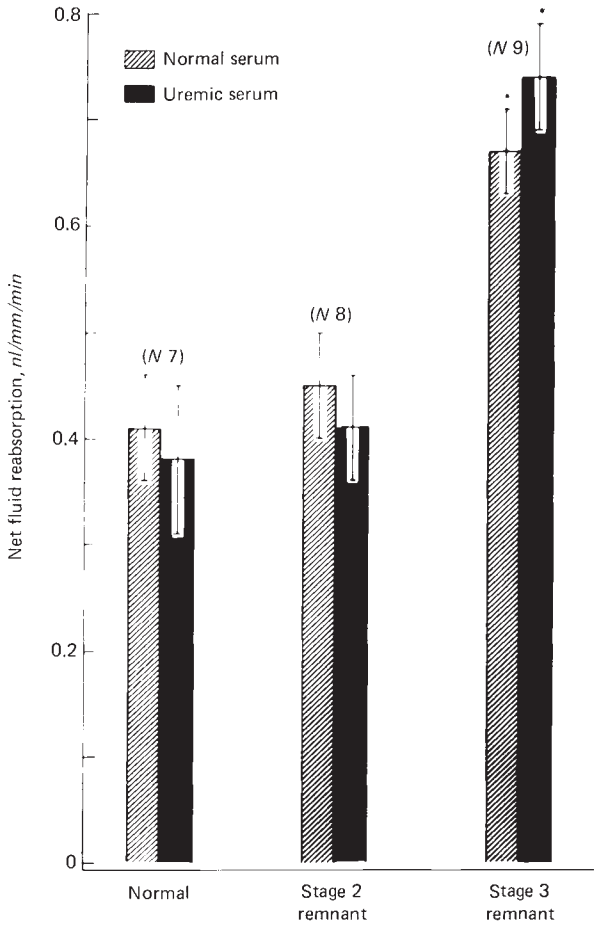

Fig. 2. *Net fluid reabsorption of superficial proximal tubules obtained from normal rabbits, from nonuremic rabbits with one remnant kidney and an intact contralateral kidney* (stage 2) *and from uremic rabbits with solitary remnant kidneys* (stage 3). Each tubule was studied in a bath of normal and uremic rabbit serum. (Reproduced with permission from [2].)

This issue was studied directly by examining the osmotic water permeability coefficient of cortical collecting tubules in the absence and presence of vasopressin [6]. In the absence of vasopressin the collecting tubules of uremic remnant kidneys were essentially impermeable to water. In contrast, the hydroosmotic response to a maximal dose of vasopressin was markedly blunted when compared to normal collecting tubules (Fig. 3).

Studies were performed to evaluate the cellular basis for this blunted hormone responsiveness. It was found that maximal stimulation of collecting tubule adenylate cyclase by vasopressin was decreased significantly. The water-permeability response to 8-bromo cAMP was also decreased and was not increased by theophylline. Taken together these data reveal alterations in the cellular response to vasopressin involving steps both prior to and subsequent to the formation of cAMP. Of interest was the observation that circulating vasopressin levels were increased markedly in the uremic rabbits [6]; this could explain the decrease in the adenylate cyclase response on the basis of down-regulation of the vasopressin receptor, but this was not studied rigorously in a dose-response fashion.

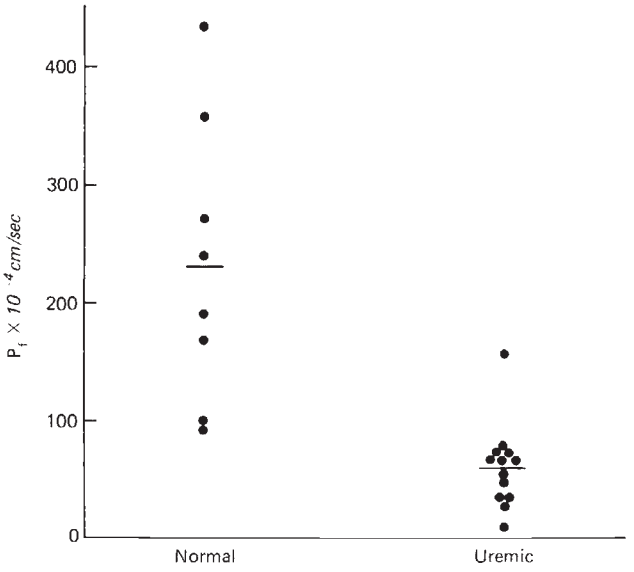

Fig. 3. *Transepithelial osmotic water permeability coefficient, P_f of normal and uremic cortical collecting tubules exposed to a maximal concentration of vasopressin.* (Reproduced with permission from [6].)

Potassium adaptation. The cortical collecting tubule is the principle nephron segment responsible for potassium secretion. Since fractional excretion of potassium rises markedly with the progression of renal failure, it was relevant to examine the mechanisms underlying this adaptation by studying the properties of the uremic collecting tubule in vitro in the absence of a uremic milieu [7]. Adaptations in the rate of net potassium secretion are illustrated in Figure 4. Uremic collecting tubules obtained from rabbits on a normal diet secreted potassium at twice the normal rate. When normal rabbits were maintained on a diet supplemented with potassium, net secretion by the collecting tubule approximately doubled. When the diet was supplemented with potassium in the uremic group, secretory rates reached six times the normal rate. The fact that these changes in transport are true adaptations is attested to by the fact that potassium secretory rates could be reduced to normal in the uremic collecting tubules if the dietary potassium intake was reduced in proportion to the reduction in GFR.

The mechanisms underlying the potassium adaptation by the collecting tubule were investigated [7]. Tubular hypertrophy was the same between groups of uremic tubules obtained from animals on different diets. Transtubular potential difference (lumen negativity) is a driving force for potassium transfer from cell to tubular lumen. Potassium loading increased the transtubular potential difference in both the normal (-29 ± 6 mV) and the uremic collecting tubules (-42 ± 5 mV), however the potential difference (PD) of normal and uremic tubules from animals on normal diets was the same (approximately -12 mV) despite a significant difference in the net potassium transport rate. Thus, while the potential difference obviously contributes to the rate of potassium secretion in uremia, it does not explain the phenomenon entirely. Similarly, circulating aldosterone levels did not correlate with potassium secretory rates since these were significantly elevated only in the uremic rabbits on a high potassium diet.

One of the factors invoked as a major determinant of potassium adaptation in uremia is the activity of Na-K-ATPase which

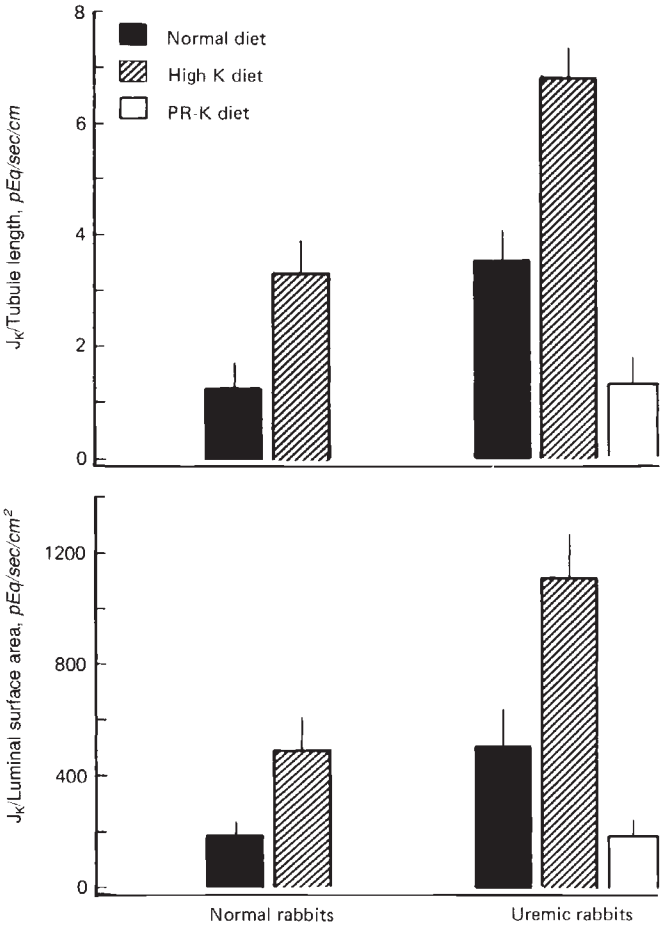

Fig. 4. *Net potassium secretion, J_K, of cortical collecting tubules from normal and uremic rabbits maintained on a normal diet, a high potassium diet, and a diet in which potassium content was reduced in proportion to the reduction in GFR (PR-K).* Potassium secretory rate is expressed per unit tubule length (*upper panel*) and per unit luminal surface area (*lower panel*). (Reproduced with permission from [7].)

is increased in the remnant kidney [8] and is increased in the normal cortical collecting tubule by potassium loading [9]. Virtually all of the studies which have linked the activity of this renal enzyme to potassium excretion have used massive potassium loading to expose the phenomenon. When we studied the relationship between net potassium secretion and the specific activity of Na-K-ATPase directly in the collecting tubule, only a moderate (twofold) increase in dietary potassium intake was used. Under these circumstances the specific activity of the enzyme was unchanged despite an approximate doubling of the rate of potassium secretion in both normal and uremic collecting tubules. This dissociation leads us to believe that, while the two phenomena occur concomitantly under certain circumstances, they are not related in a cause-and-effect manner. Potassium adaptation by the cortical collecting tubule can occur without a measurable increase in Na-K-ATPase activity.

Unifying concepts emerging from studies of isolated renal tubules in uremia

It is evident that two separable adaptive phenomena are induced in the renal tubules in states of chronic renal disease.

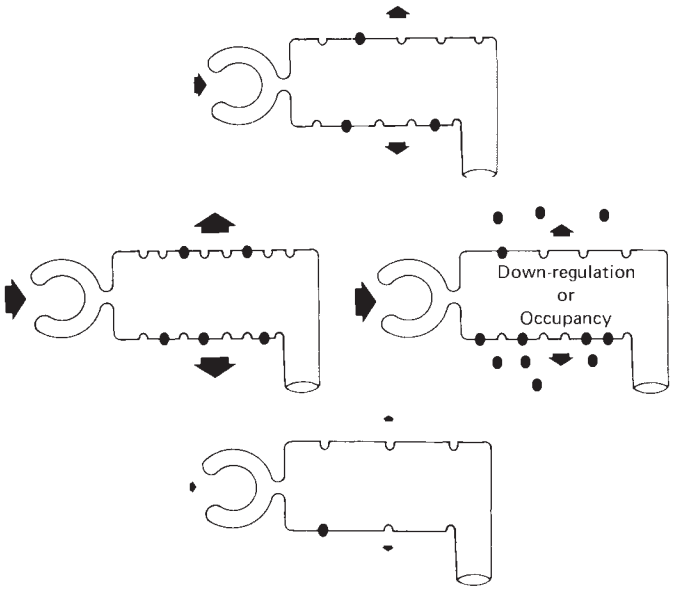

Fig. 5. *A concept of tubular adaptation in which the number of "reabsorption sites" or hormone receptors are depicted as indents on the tubule.* The *arrow size* depicts the rate of filtration or reabsorption of a given solute. The *upper* nephron is normal. The *middle two* nephrons have an increased rate of filtration. The nephron on the *left* has both an increase in reabsorption sites (with an increase in reabsorption rate) and an increase in hormone receptors so that the number of hormone-receptor complexes is increased. The nephron depicted on the *right* shows either down-regulation or occupancy of reabsorption sites and hormone receptors secondary to high circulating levels of the hormone. The *lower* nephron has a reduced filtration rate and a proportionally reduced number of reabsorption sites and hormone receptors. (Reproduced with permission from [10].)

These are *(1)* adaptations in the intrinsic rates of reabsorption which are manifested in vitro and are referred to as tubular "memory" since they reflect the reabsorptive pattern in vivo, and *(2)* adaptations in the sensitivity and responsiveness of the tubules to exogenous stimuli such as hormones. These adaptations are depicted graphically in Figure 5 [10].

Since transport rates for different solutes are increased or decreased according to the nature of the disease, the tubule can be conceived of having differing numbers of "reabsorption sites." An increase in "reabsorption sites" could refer to an increase in the number of pumps or carriers, or it could refer to an alteration in the affinity for, or the permeability of, the tubule to the solute. The term, therefore, provides a conceptual framework only. When filtered load is increased or decreased, absolute reabsorption increases or decreases in parallel leading to the maintenance of glomerulotubular balance. The number of reabsorption sites is not, however, a fixed property of the tubule but can be modulated by specific influences in vivo. Thus, an increased intrinsic reabsorptive rate can be reduced in the same tubule by any influence which decreases the number of reabsorption sites either by occupying or blocking them, by altering their affinity or by reducing their number. This concept is best demonstrated in studies on the basal rate of proximal tubular phosphate transport in which lumen-to-bath flux is increased in a uremic tubule from euparathyroid rabbits studied in a controlled nonuremic environment but is decreased in the same tubule when the animal develops secondary hyperparathyroidism [4].

An exactly parallel description of hormone sensitivity can be proposed. ("Sensitivity" refers to a right- or left-shift in the dose-response curve; "responsiveness" refers to the response to a maximal concentration of the hormone.) Under certain circumstances the sensitivity of the tubule is increased and this would correspond with an increase in the number of hormone receptors. High-circulating levels of the hormone in vivo may, however, lead to a decrease in sensitivity either by persistent occupancy or by the well-described phenomenon of down-regulation in which the number of receptors is decreased when circulating levels of the hormone increase.

It is obvious that the study of adaptations of tubular function will begin to provide many important insights into the workings of normal renal tubules. Disease imposes stresses on homeostasis which often expose processes that otherwise would remain inapparent. By manipulating experimental conditions in models of chronic renal disease, it is hoped that the nature of the individual elements controlling tubular function and the interplay between these elements will become apparent.

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